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Influence of dissolution rate on the extent and rate of bioavailability of metoprolol

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Summary

Three extended release formulations of metoprolol (95 mg metoprolol succinate) with different in vitro release rates were administered to ten healthy males (20–29 years) as single oral doses. The bioavailability properties of the three formulations were evaluated in relation to an intravenous dose (10 mg metoprolol tartrate) and an oral solution (95 mg metoprolol succinate). Both the rate and extent of metoprolol absorption were related to the drug release rate as shown by the plasma concentration-time profiles and resultant pharmacokinetic variables. Individual absorption-time profiles reflected well the corresponding in vitro release curves, showing a good correlation over the entire time interval for all three formulations. For the slowest formulations, drug absorption continued at very delayed times (24–30 h) in most individuals, confirming the good distal gastrointestinal absorption of metoprolol. A reduced bioavailability was seen with all extended release formulations compared with the solution and was probably caused by increased hepatic first-pass metabolism. Incomplete absorption may also contribute to the more markedly reduced bioavailability of the slowest formulation. Evaluation of compartmental (Wagner-Nelson, Loo-Riegelman) and noncompartmental (numerical deconvolution) methods for assessing drug absorption suggests that all three methodologies are appropriate when applied to extended release formulations of metoprolol.

Introduction

An important feature in the biopharmaceutical development of an oral extended-release preparation is to define the in vitro dissolution properties which correspond to the predetermined objectives with the product. In general this is accomplished by performing several in vivo bioavailability studies screening different formulations. Prediction of the in vivo performance by employing in vitro dissolution testing in conjunction with pharmacokinetic/pharmacodynamic modelling has also been suggested (Smolen, 1983; Leeson et al., 1985). The latter approach, however, before being undertaken requires knowledge about several properties such as in vitro/in vivo correlations, the drug's extent and site of absorption, its pharmacokinetics (elimination half-life, metabolism etc) and pharmacodynamics (dose-concentration-effect relationship).

Metoprolol, a widely used β_1-selective adrenoceptor antagonist, is rapidly and completely absorbed from the gastrointestinal tract when administered in conventional dosage forms (Regårdh et al., 1974). The systemic availability after oral administration, however, is only about 50% due to

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hepatic oxidative metabolism which is subject to genetic polymorphism (Lennard et al., 1986). Since metoprolol has a relatively short elimination half-life of 3–4 h, a simple once-daily dosage regimen of a conventional tablet is not sufficient to sustain plasma levels and a clinically effective β_1-blockade over the entire day.

The present study was performed as the basis for defining the biopharmaceutical properties of an oral once-daily metoprolol preparation. Ideally, such a formulation should provide sustained plasma concentrations which are sufficiently high to produce a clinically effective β_1-blockade throughout a 24-h dosage interval and without giving high plasma concentration peaks which might cause unwanted effects. The objectives of this study were to investigate the influence of administration rate on the bioavailability and first pass elimination (oral clearance) of the drug, to establish a relationship between the in vitro dissolution of the formulations and their corresponding absorption profile in vivo, and to compare different calculation methods for assessing the performance of the formulations in vivo.

Material and Methods

Drug formulations

Three extended-release preparations (A–C) of metoprolol succinate 95 mg (metoprolol succinate; Astra Pharmaceutical Production AB, Södertälje, Sweden) having different dissolution rates were prepared. All were based on a multiple-unit pellets system comprising a plurality of individual drug delivery units. The metoprolol succinate pellets were manufactured in a laboratory scale fluidized bed apparatus, yielding essentially spherical drug particles with a diameter of 0.4–0.5 mm. The drug pellets were coated with a nondisintegrating layer of mainly ethylcellulose 10 cps (Dow Chemicals Inc., U.S.A.) using the same equipment. The coated drug pellets were then mixed with approximately equal amounts of inert excipient granules consisting essentially of microcrystalline cellulose (F.M.C. Corp., Ireland). After addition of magnesium stearate, the mass was compressed to rapidly disintegrating tablets on a rotary press (Korsch Pharmapress 100). The different release rates of the formulations were obtained by varying the film thickness of the polymeric coating on the drug pellets.

As study references, an oral aqueous solution (SOL) of metoprolol succinate 95 mg (0.95 mg/ml) and an intravenous (i.v.) solution of metoprolol tartrate 10 mg (1 mg/ml) were used.

Subjects

10 healthy male subjects entered the study. Their ages ranged between 20–29 years (mean 24 years) and their weight between 70–86 kg (mean 78 kg). They were all judged healthy based on medical history, physical examination, ECG and clinical laboratory testing. All subjects gave written informed consent before participation. The study was conducted in accordance with the Helsinki Declaration and the study protocol was reviewed and approved by the local Ethics Committee of the University of Gothenburg and the Swedish Health Authorities.

Study design and procedures

The study was of randomized, five-way, crossover design. The subjects attended the laboratory in the morning and received each of the five treatments as a single dose at approx. 8.00 a.m. after having abstained from both food and fluids since 10.00 p.m. the previous evening. Each of the three extended-release preparations was administered together with 200 ml of tap water. The oral solution (100 ml) was taken together with 100 ml of water. The intravenous dose was infused into a forearm cubital vein at a constant rate of 1 mg/min over 10 min. For safety reasons, supine heart rate, blood pressure and ECG were registered during the infusion period. There was a washout of at least 5 days between consecutive treatment days.

Venous blood samples were collected via an indwelling catheter before drug administration and frequently for 10 and 12 h after administration of the intravenous infusion and oral solution, respectively. In addition, a 24 h sample was taken after the oral solution. For the three extended-release formulations, blood samples were taken frequently

for 14 h and additionally from 24 h up to 30 h after dosing.

Standardized meals were served 3, 5, 8 and 12 h after dosing. No alcohol or other drugs were permitted for the duration of the study.

In vitro dissolution

The in vitro dissolution of six individual tablets of each extended-release preparation was measured according to the following methods: USP dissolution apparatus No. 2 (rotating paddle) at a rotation speed of 50 or 100 rpm; 500 ml test medium at 37°C and pH 1.2 (simulated gastric juice (USP)), pH 4.0 or pH 6.8 (phosphate buffer solutions).

Plasma analysis

Blood samples for assays of metoprolol concentration in plasma were collected in Venoject® heparinised tubes. After adjustment to room temperature the samples were centrifuged and the plasma was decanted and kept frozen at −20°C until analysis. Metoprolol was determined by gas chromatography and electron capture detection (Ervik et al., 1986). The minimum determinable concentration was 10 nmol/l ($SD_{rel} \leq 10\%$).

Calculations and statistics

Disposition pharmacokinetics after i.v. administration of 10 mg metoprolol tartrate were evaluated for each subject according to an open two-compartment model by using the extended least square nonlinear regression analysis program ELSFIT (Peck et al., 1984).

Some of the pharmacokinetic variables derived after i.v. administration are given in Table 1. The intercepts (C_1, C_2) were adjusted to a bolus injection (Loo and Riegelman, 1970). The AUC was the area under the fitted plasma concentration-time curve from 0 h to infinity.

The plasma concentration-time curves after oral administration were described by the variables; maximal plasma concentration (C_{max}), time to reach C_{max} (t_{max}), plasma concentration at 24 h after dosing (C_{24}), mean residence time (MRT) and area under the plasma concentration-time curve from 0 h to infinity (AUC). The MRT was calculated according to the method of statistical moments (Riegelman and Collier, 1980). The AUC was determined by the trapezoidal rule except for values between 12 and 24 h after administration of the oral solution for which the log-trapezoidal method was applied. The remaining area from the last measurable plasma concentration ≥ 10 nmol/l (C_{last}) to infinity was calculated by the

TABLE 1

Individual pharmacokinetic variables after intravenous administration of metoprolol tartrate 10 mg in nine healthy subjects

Subject No.	C_1 (nmol/l)	C_2 (nmol/l)	λ_1 (1/h)	λ_2 (1/h)	V_c (l)	V_{area} (l)	Cl (l/h)	AUC (nmol h l^{-1})	MRT (h)
1	226	87	5.3	0.20	93	301	59	491	4.6
2	833	121	13.8	0.11	31	228	26	1132	8.4
3	709	101	9.7	0.30	36	238	71	411	2.8
4	386	99	3.5	0.19	60	243	47	619	4.3
5	65	100	1.3	0.21	177	264	56	522	4.3
7	108	88	4.2	0.20	149	315	62	475	4.9
8	275	99	7.6	0.21	78	274	59	499	4.3
9	312	99	25.7	0.26	71	285	74	394	3.7
10	346	109	16.3	0.11	64	262	30	985	8.6
Mean	362	100	9.7	0.20	84	268	54	614	5.1
SD	256	10	7.8	0.06	49	29	17	263	2.0

formula $C_{last}/\beta_{i.v.}$ assuming pure elimination. The absolute bioavailability (F) of the oral administrations was determined by the AUC ratio oral/i.v. after correction for dose. Similarly, the relative bioavailability (F_{rel}) was determined in relation to the oral solution.

To investigate the relationship between systemic availability (F) and the apparent oral clearance (Cl_o) for the different formulations the following equation was used:

$1/F = Cl_o/Q + 1$ (Somogyi et al., 1982)

where Q is the hepatic blood flow at equilibrium and Cl_o = dose/AUC. Linear regression analysis was performed on the linear plot of $1/F$ vs Cl_o to study if the model was applicable to metoprolol.

The fractional amount of drug absorbed from a given dose was calculated for each individual by using numerical deconvolution (Langenbucher, 1982). In the algorithm, plasma concentrations after i.v. administration were used as the weighing function and the oral plasma concentration data as the response function. The selected time interval was 0.25 h.

Individual absorption-time curves were also calculated by the compartmental methods according to Wagner and Nelson (1963), Loo and Riegelman (1968)/Boxenbaum and Kaplan (1975).

Moment analysis (Brockmeier et al., 1983) was applied on the individual absorption curves and cumulative in vitro dissolution profiles to calculate the mean time for absorption (MAT) and dissolution (MDT), respectively. The MAT was used to estimate the mean dissolution time in vivo using the expression: $MAT_{A,B,C} - MAT_{SOL}$. In addition MDT in vivo was estimated by the difference between mean residence times ($MRT_{A,B,C} - MRT_{SOL}$).

Full time in vitro/in vivo correlations were established for the three extended-release formulations by comparing dissolution profiles with the absorption-time curves derived from the Wagner-Nelson equation (Wagner and Nelson, 1963). The elimination rate constants determined after i.v. administration were used in the calculations.

All pharmacokinetic results are presented as mean (SD) values. Statistical significances of the linear regression analyses were determined by analysis of variance (ANOVA) and 95% confidence intervals.

Results and Discussion

All 10 subjects who were randomized completed the five treatment periods of the study. One subject, No. 6, was excluded from the pharmacokinetic analysis of the intravenous data since his plasma concentration-time curve virtually did not decline over the 10-h period studied and could thus not be evaluated according to the applied model. Administration of the oral solution to this subject resulted in high plasma concentrations and an elimination half-life of 7.7 h. It is likely that this individual can be characterized as a poor metabolizer of metoprolol, although this does not explain his results after i.v. administration. Apart from the i.v. data, the subject was included in the analysis.

All treatments were well tolerated and no adverse experience considered to be related to the the study drugs was reported during the study days.

Disposition pharmacokinetics

Pharmacokinetic variables after i.v. administration are given in Table 1. The plasma concentrations of metoprolol showed a good fit to the applied two-compartment model in nine of the 10 subjects (details of the remaining subject have been given above). The mean derived parameters and their variation were in good agreement with earlier reported results in healthy volunteers (Regårdh et al., 1974; Jordö et al., 1980). Two of the subjects, Nos 2 and 10, had markedly lower clearance and higher AUC values than the other subjects. The results indicate that these two individuals also may be classified as poor metabolizers of metoprolol.

Absorption and bioavailability after oral administration

The mean plasma concentration-time curves of metoprolol after administration of the oral solution and the three extended-release formulations

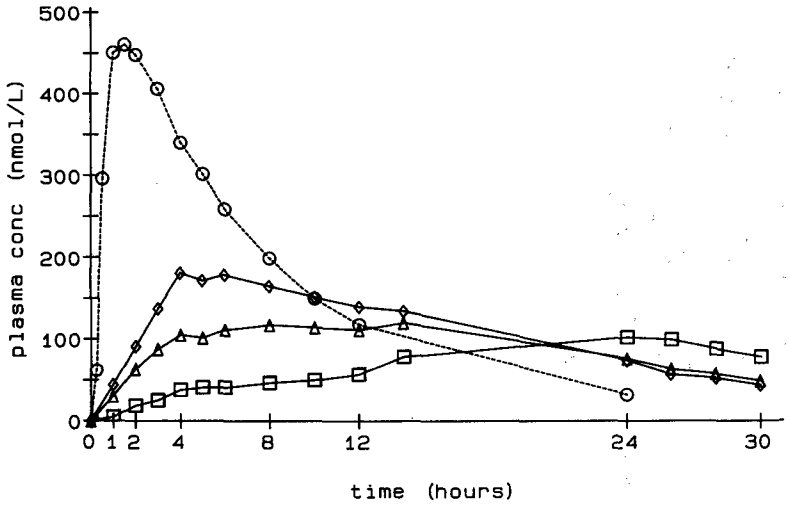

Fig. 1. Mean (n = 10) plasma concentrations of metoprolol after single dose administration of metoprolol succinate 95 mg as an oral solution (○) and three extended-release formulations A (◇), B (△) and C (□).

are shown in Fig. 1. A summary of the derived pharmacokinetic variables is given in Table 2. Individual absorption-time plots derived from numerical deconvolution are shown for four of the subjects in Fig. 2a–d.

As expected, the absorption was rapid after administration of the oral solution and completed within about 2 h in all subjects. In contrast with the extended-release preparations, each individual showed a prolonged absorption which resulted in sustained and even plasma concentration profiles with considerably reduced peak concentrations and higher plasma levels at the end of the dosage interval compared with the oral solution (Fig. 1, Table 2).

The fraction of drug absorbed between 24 h and 30 h after administration of the slowest formulation was 0.16 (0.06) of the total absorbed dose. In eight of the nine subjects this value was greater than 0.1, confirming that metoprolol is

TABLE 2

Mean (SD) pharmacokinetic variables calculated for 10 subjects after single-dose administration of metoprolol succinate 95 mg as an oral solution (SOL) and as three extended-release formulations (A–C)

Formulation	C_{max} (nmol/l)	C_{24} (nmol/l)	t_{max} (h)	MRT (h)	AUC (nmol h l^{-1})	F^b (–)	F_{rel} (–)
SOL	512	32	1.4	6.6	4266	0.48	–
	(235)	(55)	(0.5–2) [a]	(3.0)	(4123)	(0.22)	
A	192	74	6.0	12.8	3732	0.39	0.83
	(151)	(94)	(4–14)	(3.5)	(3890)	(0.20)	(0.15)
B	127	76	8.2	15.8	3148	0.34	0.77
	(105)	(82)	(2–14)	(2.5)	(3135)	(0.14)	(0.17)
C	107	102	23.4	21.4	2678	0.29	0.61
	(96)	(95)	(14–26)	(2.7)	(2663)	(0.15)	(0.07)

[a] Given as the range of individual values.
[b] Absolute bioavailability in relation to the i.v. dose.

well absorbed in distal regions of the gastrointestinal tract also when delivered at a very slow rate. For formulations A and B, absorption seemed to be completed in most individuals within about 20 and 24 h, respectively. The validity and accuracy of the numerical deconvolution results were verified by the good agreement between the end-points for the fractional absorption-time curves which were 0.47 (0.20), 0.38 (0.19), 0.34 (0.14) and 0.29 (0.15) for SOL, A, B, and C, respectively, and the F values obtained from the ratio of AUC oral/i.v. (Table 2).

The mean value of F for the oral solution, 0.48, corresponded well with previously reported results (Regårdh et al., 1974, 1983; Schaaf et al., 1987). The two subjects having the lowest clearance values after i.v. administration had the highest systemic availability of metoprolol, 0.89 (No. 2) and 0.66 (No. 10), in this panel of subjects. This less pronounced first-pass elimination in these two individuals confirms their supposed low capability of metabolizing metoprolol.

The extent of bioavailability also seemed related to the administration rate as shown by the absolute (F) and relative (F_{rel}) bioavailability values (Table 2). Possible explanations for the reduced relative bioavailability are incomplete drug release from the preparation, too slow drug release in relation to the gastrointestinal transit time or more extensive first-pass degradation when administering metoprolol at a slow rate. The impact of the latter effect was demonstrated in a previous study (John, 1990). The author reported that an intragastric or intraduodenal continuous infusion of a metoprolol solution for 13.5 h gave a reduced AUC in six subjects (average 23.7%) compared with the same dose (200 mg) given orally as a bolus dose. Thus, it is likely that greater pre-systemic elimination is the major explanation for the reduced bioavailability of metoprolol when admin-

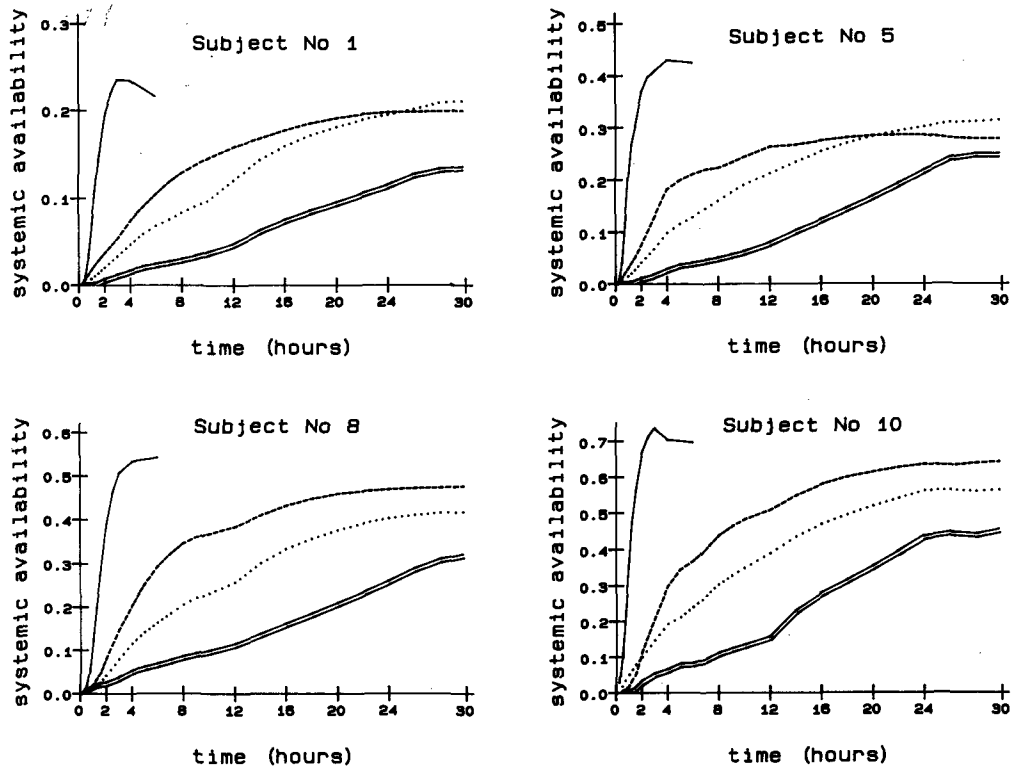

Fig. 2. (a–d) Individual profiles in 4 subjects of fractional amount of metoprolol reaching the systemic circulation at different times after administration of an oral solution (———) and formulations A (— — —), B (· · · · · ·) and C (═══). The curves were derived by numerical deconvolution using i.v. data as the weighing function (unit impulse).

istered at a slow rate, irrespective of the pharmaceutical preparation used. It should be noted, however, that total AUC values for the slowest formulations were somewhat underestimated in those cases when drug absorption continued after the last plasma sample (30 h). This could not be taken into account when calculating the remaining area under the curve.

To investigate further the effect of administration rate on the oral bioavailability and first-pass elimination of metoprolol, a plot of the reciprocal of systemic availability ($1/F$) vs oral clearance (Cl_o) for the oral solution and the three extended release formulations was made (Somogyi et al., 1982). As shown in Table 3 and Fig. 3, the correlation was good for the relationship with a statistically significant ($P < 0.001$) regression for each of the four metoprolol administrations. The 95% confidence limits of the slopes and intercepts indicate that the model is applicable to metoprolol and that hepatic first pass metabolism is the major determinant of the reduced systemic availability of all oral administrations. For the two formulations having the slowest dissolution rate, the intercept values were greater than unity (1.05 for B and 1.11 for C). This trend to higher intercept values for the slower formulations may be explained by incomplete absorption which probably contributes to the further reduced bioavailability for these two formulations.

TABLE 3

Linear regression analysis of the relationship between $1/F$ and Cl_o for three extended-release formulations (A–C) and an oral solution (SOL) of metoprolol

Formulation	Slope (95% CI) [a]	Intercept (95% CI)	r^2
SOL	0.0130 (0.0120–0.0139)	0.66 (0.48–0.83)	0.94
A	0.0128 (0.0121–0.0134)	0.84 (0.67–1.00)	0.98
B	0.0123 (0.0108–0.0138)	1.05 (0.77–1.38)	0.85
C	0.0128 (0.0118–0.0138)	1.11 (0.82–1.41)	0.93

[a] 95% confidence interval.

In vitro / in vivo correlations

The mean in vitro dissolution time values obtained at different pH and agitation rates show that drug release from all formulations is virtually independent of these two variables (Table 4). The mean cumulative dissolution profiles obtained at

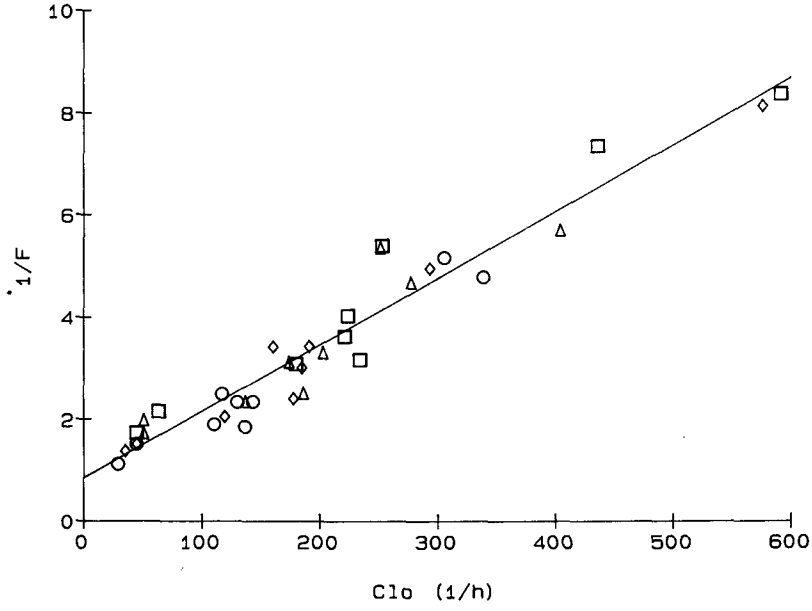

Fig. 3. Reciprocal of absolute availability ($1/F$) vs oral clearance (dose/AUC) for each individual after administration of an oral solution (○) and formulations A (◇), B (△) and C (□) of metoprolol succinate 95 mg. The connecting line ($0.013X + 0.84$) was derived from all 36 data points.

TABLE 4

Mean time for in vitro dissolution (hours) of metoprolol succinate from formulations A–C (Method: USP apparatus No. 2 (rotating paddle); 500 ml test medium at 37 °C; n = 6 tablets)

Formulation	Dissolution conditions			
	pH 1.2/100 rpm [a]	pH 4.0/100 rpm [b]	pH 6.8/100 rpm [c]	pH 6.8/50 rpm [c]
A	4.8	5.7	5.3	5.7
B	8.4	8.8	8.6	8.6
C	13.6	13.7	13.8	14.1

[a] Simulated gastric juice USP without enzymes, pH 1.2.
[b] Phosphate buffer containing NaH_2PO_4 (1 M) and H_3PO_4 (1 M), pH 4.0.
[c] Phosphate buffer containing NaH_2PO_4 (1 M) and Na_2HPO_4 (0.5 M), pH 6.8.

pH 6.8 and a rotation speed of 100 rpm are presented in Fig. 4 together with the mean absorption curves from the Wagner-Nelson calculations. The in vitro and in vivo curves followed each other rather closely over the entire time period, showing that the in vitro dissolution test method appropriately discriminated between the three formulations and mirrored their behaviour in vivo.

Fig. 5 shows a plot of the relationship between the mean dissolution times in vitro and in vivo determined from the cumulative dissolution and absorption (Wagner-Nelson) curves by statistical moment analysis. The MDT in vitro appeared to be somewhat shorter than the calculated MDT in vivo. However, linear regression analysis of the data showed a good correlation between the two

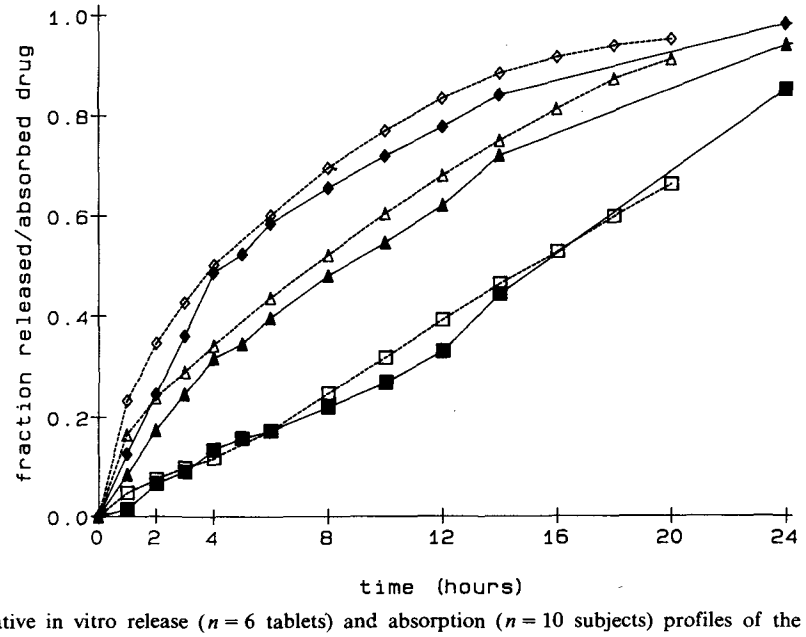

Fig. 4. Mean cumulative in vitro release ($n = 6$ tablets) and absorption ($n = 10$ subjects) profiles of the three extended-release formulations of metoprolol succinate 95 mg. The fraction absorbed drug was determined by the Wagner-Nelson method assuming complete (1.0) absorption at 30 h after dosing. In vitro dissolution method: USP apparatus No. 2; 100 rpm; phosphate buffer, pH 6.8. Empty symbols with a dashed line depict the in vitro release profiles of A (◇), B (△) and C (□). Corresponding absorption profiles are identified by the filled symbols.

variables with similar relationships for the different testing conditions.

Compartmental versus noncompartmental methods

A comparison of the individual MDT in vivo values ($MAT_{A,B,C} - MAT_{SOL}$), originating from the model-independent linear analysis (numerical deconvolution) and the compartmental methods (Wagner-Nelson and Loo-Riegelman), is presented in Table 5. The three methods were comparable as indicated by the similar in vivo dissolution times for the three preparations in most individuals. The results were also consistent with the MDT values obtained from the difference of mean residence times determined from the plasma concentration-time curves ($MRT_{A,B,C}-MRT_{SOL}$). Although the Wagner-Nelson method should be used with caution for a drug showing two-compartment disposition kinetics, the results demonstrate that the method is applicable for assessing the absorption behaviour of slowly absorbed formulations of metoprolol. In the development of new formulations, the Wagner-Nelson method is attractive because of its simplicity compared with the other methods. The Loo-Riegelman method requires intravenous data and analysis by numerical deconvolution often requires manipulation of the raw data by some smoothing procedure to eliminate the systemic noise.

Conclusions

The three investigated extended release formulations of metoprolol succinate produced sustained and even plasma concentrations over a 24-h dosage interval with an intersubject variability similar to an oral solution. Further, they all showed a reduced extent of bioavailability compared with the oral solution although to a different degree. A plot of the reciprocal of systemic availability ($1/F$) vs oral clearance (dose/AUC), suggests that hepatic first-pass metabolism is the major determinant of the reduced bioavailability for all oral administrations. However, incomplete drug absorption apparently contributed to the more pronounced reduced bioavailability of the slowest formulations.

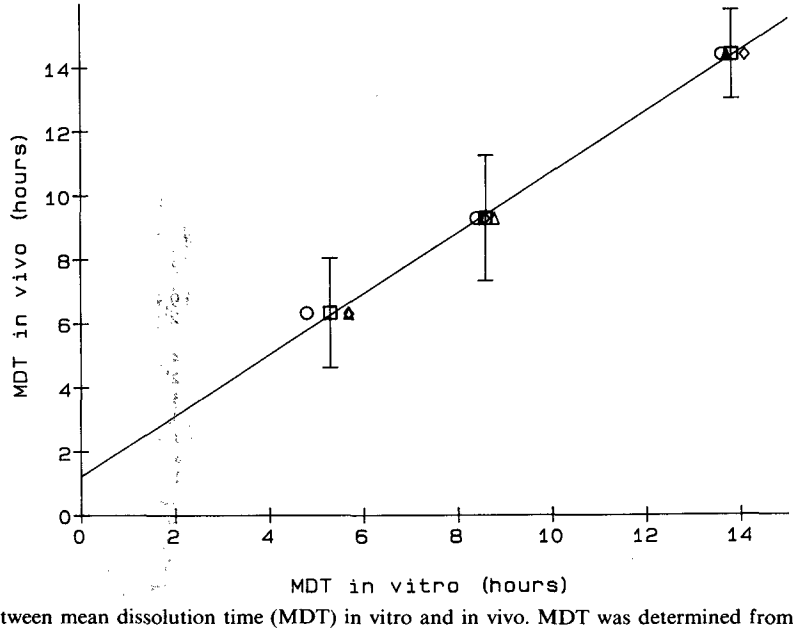

Fig. 5. Relationship between mean dissolution time (MDT) in vitro and in vivo. MDT was determined from cumulative absorption (Wagner-Nelson method) and in vitro release curves by statistical moment analysis. The line and bars (SD) represent the results obtained at pH 6.8/100 rpm. (○) pH 1.2/100 rpm: $0.92X + 1.77$, $r^2 = 0.998$; (△) pH 4.0/100 rpm: $1.01X + 0.50$, $r^2 = 0.999$; (□) pH 6.8/100 rpm: $0.95X + 1.21$, $r^2 = 0.999$; (◇) pH 6.8/50 rpm: $0.96X + 0.95$, $r^2 = 0.999$.

Individual absorption-time profiles corresponded well to the in vitro release curves over the entire time interval for all three formulations. Drug absorption seemed to continue at very late times (24–30 h) in most individuals after administration of the slowest formulations, confirming the good absorption properties of metoprolol throughout the gastrointestinal tract. The good in vitro/in vivo correlation results further suggest that plasma concentration profiles could be predicted from in vitro dissolution data for any metoprolol extended release preparation of this type.

Finally, the inclusion of both an i.v. dose and an oral solution as study references, enabled a

TABLE 5

Mean dissolution times (MDT) in vivo determined from individual absorption-time curves and related mean absorption times ($MAT_{A,B,C} - MAT_{SOL}$). A comparison between results obtained by numerical deconvolution (DEC), the Wagner-Nelson (W-N) method, the Loo-Riegelmann (L-R) method and by the difference of mean residence times ($MRT_{A,B,C} - MRT_{SOL}$) determined from plasma concentration-time curves (ΔMRT)

Subject No.	Formulation	MDT in vivo (h)			
		DEC	W-N	L-R	ΔMRT
1	A	6.5	6.5	7.5	6.8
2		6.5	5.8	4.9	5.1
3		4.9	4.8	4.7	3.7
4		8.6	8.1	8.8	8.1
5		3.4	3.5	2.5	3.5
7		8.6	8.6	8.6	8.8
8		5.5	5.4	4.8	5.3
9		8.5	8.2	8.0	7.6
10		6.4	6.1	6.3	6.7
Mean		6.5	6.3	6.2	6.2
SD		1.8	1.7	2.1	1.9
1	B	10.3	10.1	11.2	10.6
2		6.1	5.6	4.6	4.7
3		11.3	10.7	10.5	10.2
4		9.8	9.3	9.9	9.3
5		8.6	8.5	7.2	8.9
7		11.8	11.7	11.5	12.0
8		8.7	8.4	7.9	8.3
9		12.0	11.5	11.1	11.3
10		8.1	7.8	7.9	8.5
Mean		9.6	9.3	9.1	9.3
SD		2.0	2.0	2.3	2.1
1	C	14.3	13.8	14.8	14.9
2		15.4	14.3	12.9	14.3
3		14.6	13.8	13.4	13.8
4		14.2	13.7	13.6	14.1
5		14.9	14.1	13.2	14.5
7		16.8	16.3	16.0	17.2
8		14.2	13.7	12.6	14.3
9		17.9	17.2	16.0	17.7
10		13.4	12.9	12.5	14.0
Mean		15.1	14.4	13.9	15.0
SD		1.4	1.4	1.4	1.4

comparison of different methodologies for assessing the absorption and in vivo dissolution characteristics of the experimental formulations. Similar absorption profiles and mean time values for absorption and in vivo dissolution were obtained for all formulations when applying the Wagner-Nelson method, the Loo-Riegelman method or numerical deconvolution, in combination with statistical moment analysis. The evaluation suggests that all three methodologies are appropriate and that it is justified to use the more simple Wagner-Nelson method in the biopharmaceutical evaluation of extended release formulations of metoprolol.

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